PSJ14 Janssen Opp Exh 35 – JAN-MS-02043301

Janssen Research & Development, L.L.C.

Regulatory Affairs **Record of Contact**

Date of Contact: 05 August 2013

Date of Report: 27 August 2013

Health Authority/Division:
Center for Drug Evaluation and Research/Division of Anesthesia, Analgesia, and Addiction Products

Product: NUCYNTA ER

NDA No.: 200533

Health Authority Contact:
Name: Dominic Chiapperino, PhD
Title: Senior Regulatory Health Project Manager (DAAAP)

Prepared by:
Name: Tania Hillmer, MS, RAC
Title: Associate Director, Regulatory Affairs

Health Authority Attendees:
Name: Bob A. Rappaport, MD
Title: Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Name: Sharon H. Hertz, MD
Title: Deputy Director, DAAAP

Name: Joshua Lloyd, M.D.
Title: Clinical Team Leader, DAAAP

Name: Jin Chen, MD
Title: Medical Officer, DAAAP

Name: Yun Xu, PhD
Title: Team Leader, Division of Clinical Pharmacology II (DCP II)

Name: David J. Lee
Title: Clinical Pharmacology Reviewer, DCP-II

Name: James Tolliver, PhD
Title: Pharmacologist, CSS

Name: Prasad Peri, PhD
Title: Branch Chief, Branch VIII, ONDQA

Name: Julia Pinto, PhD
Title: CMC Lead, Branch VIII, ONDQA

Company Attendees:
Name: Mila Etropolski, MD
Title: Senior Director, Compound Development Team Leader

Name: Michael Kaufman, RPh
Title: Director, Global Regulatory Affairs

Name: David Biondi, DO
Title: Therapeutic Area Lead, Analgesics, US Medical Affairs

Name: Jeff Kinzer, PhD
Title: Associate Director, Global Regulatory Affairs -CMC

Name: Hany Rofael, MD, PhD
Title: Associate Director, Clinical Development, US Medical Affairs

Name: Douglas Shapiro, MD, PhD
Title: Senior Director, Clinical Leader

Name: Gary J. Vorsanger, PhD, MD
Title: Senior Director, Clinical Development, Central Nervous System, US Medical Affairs

Name: Lalitha Mahadavan, MB ChB, MRCS(Ed), MD, MFPM
Title: GMS Physician, Global Medical

Janssen Research & Development, L.L.C.

Name: Cynthia Kornegay, PhD
Title: Epidemiologist Team Lead, DEPI-II, OSE

Name: Alex Secora, MPH
Title: Epidemiologist, OSE, DEPI II

Name: Jamie Wilkins Parker, PharmD
Title: Team Leader, DMEPA, OSE

Name: Vicky Borders-Hemphill, PharmD
Title: Safety Evaluator, DMEPA

Name: Mark Liberatore, PharmD
Title: Safety Regulatory Project Manager, OSE

Safety
Name: Yinka Williams, PhD
Title: Senior Scientific Director, CMC Leader

Name: Peter Zannikos, PhD
Title: Director, Clinical Pharmacology

Name: Holly Patel
Title: Senior Associate, Regulatory Affairs

Grünenthal GmbH Attendees:
Name: Ronald Rosenburg, MD
Title: International Clinical Lead

Name: Alice Ebel
Title: Senior Manager, Global Regulatory Affairs

Subject: NUCYNTA ER Type C Sponsor Meeting Minutes

On 05 August 2013, a teleconference was held between representatives of Janssen Research & Development, LLC (JRD), Grünenthal GmbH and the FDA to discuss potential tapentadol chronic (ER) abuse deterrence-related labeling claims. On 02 August 2013, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) provided us with preliminary comments to our meeting questions that were submitted on 12 June 2013. The clarification questions discussed at the 05 August 2013 meeting are outlined below. The FDA's 02 August 2013 remaining responses to our meeting questions were not subject to further discussion.

Sponsor's Briefing Book Question 1
Does the Agency agree that the data described in the Briefing Document are sufficient to support the filing and potential approval of an abuse deterrent labeling claim for NUCYNTA ER?

FDA Response:
You conducted the following studies to evaluate the abuse-deterrent properties of Nucynta ER:
1) an in vitro abuse-deterrent assessment
2) a pharmacokinetic study (Clinical Study Report HP5503/62)
3) two bench-top studies (Protocol R331333PAI0002) for preparation of an intravenous solution and Protocol R331333PAI0001 for manipulation of the test product for intranasal abuse).

Confidential

No human abuse potential studies were conducted.

A preliminary review of the data provided shows that none of these studies are robust and compelling enough to support abuse-deterrent Tier 1, 2, or 3 labeling claims for various routes of administration. (See response to Question 2 below).

The data provided are not sufficient to support an abuse-deterrent claim. Data from in vitro studies (Category 1), pharmacokinetic studies (Category 2), and human abuse potential studies (Category 3) are required to support abuse-deterrent labeling claims (Tier 1, 2, or 3 claims), as described in the January 2013, Guidance for Industry: *Abuse-Deterrent Opioids - Evaluation and Labeling*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf>

Category 1 data alone are not sufficient to support a Tier 1 claim without additional supportive Category 2 or 3 data to provide context. To support a Tier 3 claim, data from Categories 1, 2, and 3 are required.

Discussion:

FDA informed the Sponsor that data from all three categories (1, 2 and 3) needs to be obtained in order to get any Tier claims, including Tier 1. The two studies (Columbia) provided to the FDA in NDA 200533 are considered bench top studies and Tier 3 studies should consist of human abuse potential studies which demonstrate a reduction in abuse potential and PK studies. Since Tier 1 requires data from Category 1, 2 and 3, Sponsor needs to conduct more than *in vitro* studies to get a Tier 1 claim.

FDA informed that the Sponsor needs to select a specific route of administration for which it wants to claim abuse deterrence and provide robust study data to support the claim. Routes of administration to study may include chewing, nasal insufflation of a crushed tablet, and intravenous use. For studies with intranasal route, FDA is concerned with effects in humans and adverse events must be taken into account for these types of studies. Studies with intravenous route would have to be supported by *in vitro* data and not human data due to safety concerns.

Sponsor's Briefing Book Question 2

In the Sponsor's opinion, laboratory analytic data (Category 1) and pharmacokinetic studies of tapentadol either chewed or taken together with ethanol (Category 2), along with data on tampering by experienced opioid abusers (Category 3), and postmarketing surveillance data (Category 4) provide sufficient evidence to support the filing and potential approval of an abuse deterrent labeling claim for NUCYNTA ER. Does the Agency agree that the data support labeling consistent with either a Tier 1 or Tier 2 claim? If not what additional data would be required?

Confidential

FDA Response :
No, we do not agree. The data provided are not sufficient to provide support for either Tier 1 or Tier 2 abuse-deterrent labeling claims.

A preliminary review of the in vitro abuse-deterrent assessment of Nucynta ER tablets, as summarized in the meeting briefing package dated June 5, 2013, and submitted under NDA 200-533 in November 2009, shows that these studies are not robust, complete, or sufficiently compelling to support abuse-deterrent labeling claims. The following comments describe the kind of data that may be sufficient to support abuse-deterrent labeling claims:

1. **To evaluate resistance to chewing, in addition to results from a standardized breaking force tester to demonstrate tablet hardness and a chewing simulation study, provide data from appropriately conducted Category 2 (pharmacokinetic) and possibly Category 3 (human abuse potential studies with pharmacokinetic (PK) and pharmacodynamic (PD) endpoints) studies.**

2. **To describe resistance to cutting, the tests using a "custom-made machine that allows the use of different blades" are not sufficient. You must provide the results of attempts to cut Nucynta ER tablets using tools such as various knives (e.g., chef's knife), box cutters, and pliers. In the event that Nucynta ER tablets can be cut into pieces, dissolution studies and a pharmacokinetic study may be appropriate to determine the effect of the cutting on tapentadol release rates.**

   Sponsor's Request for Clarification of Question 2:
   The custom-made cutting machine used in resistance to cutting tests was implemented to ensure objectivity in the comparisons between a tamper-resistant and non-tamper-resistant tablet. The use of a chef's knife, box cutters, pliers, etc. would introduce subjectivity. Additionally, it seems to us that such testing would need to be performed in laboratory environment. Is this the Agency's understanding as well?

Discussion:
The Sponsor asked if the tablet cutting studies should be conducted in a laboratory setting. The FDA confirmed that this should be the case but the use of a cutting machine is objective and can't predict subjective human behavior. The cutting studies should be done using knives, box cutters, and pliers to cut the product into pieces and should measure the number of cut pieces obtained and the ease of cutting the product.

FDA Response to Question 2 (continued)

Confidential

3. **Data from use of a pill crusher and hammer are not sufficient to evaluate whether the formulation can be manipulated for the purpose of snorting. Additional studies are required to evaluate the grinding of the formulation into a range of particle sizes that might be insufflated. This would include grinding for various lengths of time (e.g., 1, 2, 4, 6, 8, 10, and 20 minutes), with the use of a coffee grinder, with subsequent determination of particle size distribution. An in vivo human abuse liability study evaluating the effects of snorting on PK and PD endpoints is necessary to evaluate whether the formulation is potentially abuse-deterrent by this route of administration.**

4. **To demonstrate that Nucynta ER tablets are resistant to manipulation by smoking, studies must be conducted to determine the thermal stability, vaporization temperature, and decomposition temperatures for tapentadol base and salt forms.**

5. **The study that examined making a preparation of tapentadol for intravenous (IV) injection from a hammered Nucynta ER tablet suggests that it may be possible, at least under the conditions of this study, to make such a solution for the purposes of abuse. Provide additional details, such as the method used to draw the aqueous solution into the syringe and the amount of fluid retrieved. This study should be expanded to examine the formation of an injectable solution by exposing the hammered tablet to water (1, 2, and 5 mL) preheated to 95°C (i.e., not boiling) for various extraction intervals ranging from 1 to 10 minutes.**

6. **The study examining the formation of a suitable preparation for IV injection using a ground tablet should also be expanded to include use of preheated 95°C water as solvent, with and without agitation, and with extraction times of 0.5, 1, 2, and 5 minutes. The possibility that a difference exists in the time to extract a sufficient amount of tapentadol compared to the dissolution of the matrix resulting in increased viscosity should be considered.**

7. **Provide a detailed particle size distribution for ground Nucynta ER tablets using various coffee grinders or other tools and not just information on the amount of material with a particle size of >2 mm. In addition, detailed particle size distributions should be provided for various grinding times (e.g., 2, 4, 6, 8, 10, and 20 minutes). Include this information in the overall assessment of possible deterrent effects to insufflation.**

8. **Extraction studies demonstrated high levels of tapentadol extraction after 5 minutes (only time point provided) of exposure of a ground Nucynta ER tablet to boiling water, 0.1 N HCl, 0.1N NaOH, or 40% ethanol. Evaluate extraction under the same conditions using intact and hammered Nucynta tablets. In addition, evaluate earlier time points for all three**

Confidential

samples (i.e., intact, hammered, and ground). Preheat solvents to 95°C and conduct the extractions in the presence and absence of agitation.

The Tier 2 pharmacokinetic study designated "Clinical Study Report HP5503/62 (R331333-PAI-1047)" is neither sufficiently robust nor compelling to support a Tier 2 claim with regard to any mastication-related abuse-deterrent effects of Nucynta ER tablets. The study includes just two treatment arms, namely 100 mg tapentadol TR PR (Nucynta ER) tablet masticated, followed by swallowing, and 100 mg tapentadol IR tablet swallowed without mastication. We have the following comments and concerns regarding this study:

1. **A detailed description of how the Nucynta ER tablets are to be chewed has not been provided.**

2. **The study design did not compare the pharmacokinetics of tapentadol following "normal" versus "vigorous" chewing, both of which need to be described.**

3. **An intact Nucynta ER tablet treatment arm was not included in the study for use as a reference for determining the degree of compromise of the ER properties following mastication.**

4. **Consider conducting an alternative pharmacokinetic study that addresses how mastication of Nucynta ER tablets may affect the pharmacokinetic parameters of tapentadol. This study should include an intact swallowed (not chewed) Nucynta ER arm, as well as treatment arms of "normally" chewed and "vigorously" chewed Nucynta ER and a Nucynta IR swallowed arm. Include detailed information about the instructions provided to subjects regarding normal and vigorous chewing. In the final study report, document the allowed chewing time as well as the actual chewing times for each subject. Also, provide any information regarding ease and difficulty of chewing and any chewing-related negative outcomes. We are willing to review and comment on a detailed, complete protocol prior to starting the study.**

Sponsor's Request for Clarification of Question 2 :

Based on the Agency's responses to Question 2, it appears that comparison to a non-tamper resistant tablet as a control is not necessary. Does the Agency concur with this assessment? If not, what type of control does the Agency recommend?

Discussion:

The Sponsor will need to recommend the product it would like to use as a control and provide a rationale to the FDA. IR as a comparator is plausible as it also shows the innate properties of the tapentadol molecule but FDA is interested in having a comparison of an intact ER product. If there is no exact match, Janssen could consider multiple comparators and suggest to FDA. FDA is

Confidential

willing to review our proposed protocols and may respond with feedback in 60-90 day timeframe but cannot guarantee this timeframe.

Sponsor's Briefing Book Question 4
Question 4. The NUCYNTA ER formulation was developed as a tamper-resistant product to deter abuse. NUCYNTA ER has only been marketed in the US with this formulation ie, there are no data available on the abuse of NUCYNTA ER without this formulation. Considering that postmarketing data for the tapentadol molecule (2 years for NUCYNTA ER and 4 years for NUCYNTA [tapentadol IR]) demonstrate, in general, a low rate of actual abuse in the community, what additional evidence would be needed to support a Tier 4 claim for NUCYNTA ER?

FDA Response :
The low rate of abuse of both tapentadol IR and ER in the community is promising, but the data do not yet provide sufficient evidence to confer a Tier 4 claim for Nucynta ER. At this point in time, it is unclear whether the relatively low amount of abuse detected is due to a low level of awareness of the drug as a consequence of its short marketing history, low utilization, reduced opioid receptor affinity of the tapentadol molecule, or the tamper-resistant characteristics of the extended-release formulation.

Due to the lack of a non-abuse-deterrent comparator, detecting meaningful change in the level of community abuse is challenging. You have chosen adequate data sources to depict the current extent of abuse in the community, but the limited time frame each data source portrays is insufficient to characterize the abuse profile of Nucynta ER. To determine if the current trend remains stable over time, continued surveillance and monitoring of Nucynta ER is necessary. The amount of data needed to determine if a trend is stable varies by situation, and the low utilization level for Nucynta ER may extend that time period. Additionally, the data must be able to show that the smaller amount of abuse in the community is contingent on the drug formulation, and not due to its low utilization or to innate properties of the molecule itself.

Sponsor's Request for Clarification of Question 4 (05 August 2013):
In the Agency's response, it is stated "the data must be able to show that the smaller amount of abuse in the community is contingent on the drug formulation, and not due to its low utilization or to innate properties of the molecule itself".

In addition, the Agency responded that "due to the lack of a non-abuse-deterrent comparator detecting meaningful change of abuse in the community is challenging". If one were to consider the IR formulation as a comparator in lieu of a non-abuse-deterrent formulation (ADF) and if current low rates of abuse were to continue for both formulations (IR and ER) despite increased utilization and awareness in the community, it still may not be possible to demonstrate a meaningful reduction in abuse by the ADF because rates are quite low.

Confidential

This inability to demonstrate a reduction in abuse by ADF may be due to the inherent properties of the molecule, which in combination with the increased challenges for the ER tablet that contains higher doses may render the combination simply not desirable by abusers.

If this is the case, does FDA have any suggestions on appropriate studies that could be undertaken to demonstrate "that the smaller amount of abuse in the community is contingent on the drug formulation"?

Moreover, given the FDA comment that "you have chosen adequate data sources to depict the current extent of abuse in the community", if it were not feasible to design studies that could demonstrate an effect by the ADF, what type of language might be considered in the label to reflect these findings?

Discussion:

Since the rate of abuse obtained from RADARS for IR and ER formulation is low, it would be very difficult to show abuse reduction with ER use in post-marketing data. FDA acknowledged that we are a unique situation to try and separate the ER formulation from the drug substance. The FDA recommended that Janssen does exploratory research including use patterns and overlap with other opioids on how the product is being used to select a meaningful comparator. We will compare IR and ER and then look at other comparators that offer similar therapeutic patterns.

Action Items:

- ***In vitro* data is not sufficient enough for a Tier 1 labeling claim. Data from Category 2 and 3 are needed.**
- **The studies should focus on the route of administration and provide supportive data to show abuse deterrence.**
- **The FDA does not recommend in vivo testing for intravenous studies and in vitro studies is the preferred method.**
- **Studies focused on manipulation tablets, e.g. resistance to cutting, the studies should be conducted in a laboratory setting using objective controls.**
- **When selecting a comparator for human abuse studies, we could use NUCYNTA IR, NUCYNTA ER (non-TRF), or something similar to Oxycontin ER. We need to propose our comparator selection to the FDA with a rationale and the FDA will try to respond on our proposals and submitted protocols for review within 90 days but there is no guarantee.**

Confidential